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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/734,613	12/13/2000	Marianne Bruggemann	37945-0009	3627

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/734,613	BRUGGEMANN, MARIANNE	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. As requested, applicant's response and the declaration by Dr. Gonzalez-Fernandez filed on 1/29/04 have been considered. As noted in the advisory action mailed on , the amendment filed on 1/29/04 has been entered. Claims 1-13, and 16-29 have been canceled and new claims 35-62 have been entered. Claims 35-62 are therefore pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Priority

Previous office actions have indicated that the applicant has not filed a certified copy of the GB 9823930.4 application as required by 35 U.S.C. 119(b). In the absence of a certified copy of the priority document, the effective filing date of the instant application is November 3, 1999.

Claim Rejections - 35 USC § 103

The rejection of claims 35-62 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,162,963 (12/19/00), filed on 6/5/95, and hereafter referred to as Kucherlapati et al., in view of Mendez et al. (1997) Nat. Genet., Vol. 15, 146-156 and Popov et al. (1996) Gene, Vo. 177, 195-201 is maintained. Applicant's arguments and the declaration by Dr. Gonzalez Fernandez have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant reiterates their previous argument that the in order to make a *prima facie* case of obviousness the office must provide specific evidence that the reference(s) teach each element of the claimed invention and that there exists suggestion/motivation to combine the references, citing *In re Vaeck, I re Dow Chemical Co.*, and *W.L. Gore v. Garlock, Inc.* The applicant also states that the evidentiary support must be based on the contents of the prior art and not rest on conclusory statements or subjective beliefs, citing *In re Lee.* These arguments have been addressed previously. As discussed in the previous response, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Further, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). In the determination of

obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. Finally, please note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988). The previous office action provided a detailed description of where the claim limitations are taught or suggested by the combination of Kucherlapati et al., Mendez et al., and Popov et al. and provided specific motivation derived from the express teachings of Kucherlapati et al. and Popov et al. for combining the teaching of the prior art to arrive at applicant's claimed invention, see paper no. 15, pages 4-6.

The declaration by Dr. Gonzalez Fernandez also reiterates applicant's previous arguments that Kucherlapati does not actually make transgenic mice that have polynucleotides encoding human lambda light chains, that Mendez et al. also does not teach transgenic mice with human lambda light chains, and that while Popov does teach the human Ig lambda YAC, Popov does not provide a concrete example of a transgenic mouse that comprises human Ig lambda chains or teach the proportion of human lambda light chain containing antibodies as compared to endogenous kappa or human kappa light chain containing antibodies.

In response to arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in

the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). In the instant rejection, the office is aware that none of Kucherlapati, Mendez, and Popov individually teach all the elements of the invention as claimed. Therefore, these references have been cited in a 103 rejection. The previous office action cited Kucherlapati et al. for teaching methods of making transgenic mice which comprise various germline segments of the human Ig loci in order to produce mice capable of reproducing the normal human antibody repertoire in response to antigen (Kucherlapati, columns 3-4). In particular, Kucherlapati teaches that transgenic mice can be produced from murine embryonic stem cells modified to include YACs using spheroplast fusion techniques (Kucherlapati et al., columns 13-16). Specifically, Kucherlapati teaches that a number of different transgenic mice can be produced using their methods including mice which have one or both of the murine endogenous light chain and/or heavy chain loci inactivated by homologous recombination, and which further contain human immunoglobulin heavy chain and/or human light chain genes (Kucherlapati et al., columns 11-12). Kucherlapati et al. further teaches that the human light chain genes can be either human kappa light chain genes or human lambda light chain genes or both kappa and lambda light chain genes (Kucherlapati et al., column 11, lines 30-36). Kucherlapati et al. further teaches various human heavy chain and light chain YACs useful for making transgenic mice (Kucherlapati, columns 29-33). Finally, Kucherlapati et al. provides particular motivation for making a mouse with disrupted expression of both endogenous Ig heavy and light chain genes, and which comprises human heavy chain, kappa light chain, and lambda light chain loci by teaching that such a mouse, ".. would allow for

the production of purely human antibody molecules without the production of host of host/ human chimeric antibodies" (Kucherlapati et l., column 11, lines 30-36). Therefore, while not specifically exemplifying the production of a human lambda light chain transgenic mouse, Kucherlapati et al. provides substantial teachings as to how to make human immunoglobulin light chain transgenic mice using YACs and clearly suggests making a human lambda light chain transgenic mouse. Mendez et al. was cited to supplement Kucherlapati et al. by teaching transgenic mice which have disrupted endogenous Ig heavy chain and light chain loci, and which further have incorporated YACs comprising contiguous germline segments of the human Ig heavy chain and kappa light chain loci (Mendez et al., pages 146 and 154-155). In particular, Mendez et al. teaches that in mice with one allele of the smaller Ig YACs, an equal distribution of human kappa and murine lambda light chain gene expression was observed (Mendez et al., page 153, column 1). Mendez et al. also teaches that human antibody diversity and repertoire in the xenomice strains recapitulates that seen in humans (Mendez et al., pages 153-154). It was further noted that the human Ig heavy chain YAC utilized by Mendez includes Cμ, Cδ, and Cγ genes (Mendez et al., page 148). Mendez et al. was not cited to teach the incorporation of human lambda light chains genes, but rather to supplement the teachings of Kucherlapati regarding the production of transgenic mice which have disrupted endogenous Ig heavy chain and light chain loci, and which further have incorporated YACs comprising contiguous germline segments of the human Ig heavy chain and kappa light chain loci. Popov et al. was cited to supplement Kucherlapati et al. by teaching the construction of a 420 kb YAC which contains 380 kb of the unrearranged germline human Ig lambda light chain locus (Popov et al., page 195). The YAC described by Popov is the exact YAC used by applicants. Popov et al. further provides

motivation for using the YAC to produce transgenic mice useful for structure-function studies of the human Ig lambda locus (Popov et al., page 200, column 2). Popov et al. therefore supplies the essential teachings of the human lambda YAC that are missing from Kucherlapati and Mendez. Kucherlapati et al. and Mendez provide all the necessary disclosure for making transgenic mice using YACs and both Kucherlapati et al. and Popov et al. suggest making a human lambda light chain transgenic mouse. Thus, based on the motivation provided by Kucherlapati to make transgenic mice comprising germline segments of the human Ig lambda light chain loci, and the motivation provided by Popov et al. to use a 420 kb YAC comprising 380 kb of the human lambda light chain loci to make transgenic mice, it would have been *prima facie* obvious to the skilled artisan to use the 420 kb YAC described by Popov in the methods of making transgenic mice taught by Kucherlapati et al.. Further, based on the successful use of the methods taught by Kucherlapati to produce human Ig transgenic mice as taught by Mendez et al., the skilled artisan would have had a reasonable expectation of success in using the YAC taught by Popov et al. to introduce human lambda light chain genes into the germline of a mouse. As noted above, obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

Regarding the ratio of human lambda light chains to endogenous kappa or human kappa light chains, it is reiterated that Mendez et al. shows that in Xenomouse I, mice which comprise a human Ig heavy chain YAC and a human kappa chain YAC have an equal distribution of human kappa light chains and murine lambda light chain in the antibody repertoire (Mendez et al., page 153, column 1). The applicant argues that these results are not comparable to the instant claims

because human kappa light chain genes were used not human lambda light chain genes. The applicant also states that since a different strain of mice with larger YACs has a more "mouse-like" ratio, that the expectation provided by Mendez would be that larger human Ig YACs would have mouse-like expression not human-like expression. However, as pointed out in the previous office action, the kappa light chain YAC used in xenomouse I was close in size to the 380kb YAC of Popov et al. The YAC used in xenomouse II is substantially larger than that taught by Popov, >800 kb versus 380 kb. Thus, since the light chain YAC taught by Popov is close is size to the kappa light chain YAC used in xenomouse I, the expectation based on the Mendez results with xenomouse I would be that the use of a small light chain YAC would yield more human-like ratios of kappa and lambda light chain containing antibodies. In addition, while xenomouse I does indeed have a human kappa light chain loci and not a lambda locus as claimed, the fact that expression of human kappa in mice shifted the light chain ratio towards a human ratio, despite the fact that mice predominantly express kappa light chains, provides a reasonable expectation that expression of human lambda light chain would likewise shift the light ratio towards a human ratio.

The applicant further argues that an obviousness rejection can be overcome by a showing that (i) there are elements not taught by the references, (ii) there is a teaching away or no reasonable expectation of success, or (iii) the applicants have demonstrated unexpected results, citing *U.S. v. Adams Gillette Co.* v *S.C. Johnson & Son, Inc.*, and *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*. Applicant's arguments regarding the specific teachings of the references and expectation of success have been addressed in the preceding paragraphs. Regarding applicant's allegation of "unexpected results", the evidence in the form the declaration

by Dr. Gonzalez Fernandez has been fully considered. Please note that whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980). The specification provides working examples which exclusively utilize a single human Ig lambda light chain YAC. This YAC is the same YAC disclosed by Popov et al. and is a "small" YAC comprising 380 kb of unrearranged human lambda light chain genomic DNA comprising all V lambda genes of cluster A, the J lambda- C lambda segments and the 3' enhancer. While the specification discloses that transgenic mice made using this YAC produce antibodies which have an approximately equal proportion of human lambda light chain and murine kappa light chain containing antibodies, neither the specification nor the declaration provides any evidence regarding the expression pattern in transgenic mice made using any other YAC or comprising any other combination of unrearranged or rearranged human Ig lambda genes. The claims as written are broad. Independent claims 35 and 48 for instance simply read on a transgenic mouse comprising human Ig Lambda genes which reads on any rearranged or unrearranged human Ig lambda gene containing DNA. Claim 41 reads on transgenic mice made using any human Ig lambda YAC. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The applicant's results discussed by Dr. Gonzalez Fernandez, which are limited to transgenic mice whose genome contains a YAC comprising 380 kb of unrearranged human lambda light chain genomic DNA comprising all V

lambda genes of cluster A, the J lambda- C lambda segments and the 3' enhancer, are therefore not commensurate in scope with the breadth of the claims.

In addition, the MPEP states that when an applicant submits evidence traversing a rejection, the examiner must reconsider the patentability of the claimed invention. The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). However, the submission of objective evidence of patentability does not mandate a conclusion of patentability in and of itself. *In re Chupp*, 816 F.2d 643, 2 USPQ2d 1437 (Fed. Cir. 1987). Facts established by rebuttal evidence must be evaluated along with the facts on which the conclusion of a *prima facie* case was reached, not against the conclusion itself. *In re Eli Lilly*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990). Evidence of unexpected results must be weighed against evidence supporting prima facie obviousness in making a final determination of the obviousness of the claimed invention. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978). In the instant case, the evidence provided is in the form of a declaration by Dr. Gonzalez Fernandez. Dr. Gonzalez Fernandez states that since it was known in the art that approximately 95% of antibodies produced in normal mice comprise kappa light chains while only 5% of antibodies comprise lambda light chains, applicant's finding that a transgenic mouse comprising a human lambda light chain locus produced antibodies which almost equal usage of lambda versus kappa light chains is unexpected and surprising. Dr. Gonzalez Fernandez also reiterates the applicant's argument that since Mendez teaches that Xenomouse II demonstrated more "mouse-like" ratios of kappa and lambda light chains, the skilled artisan would have expected "mouse-like" rather

than "human-like" ratios in transgenic mouse comprising large Ig YACs. However, as discussed above, Mendez in fact shows that while the larger Ig YAC mice have a more "mouse-like" expression pattern, expression of kappa and lambda chains in mice with smaller Ig YACs was equal, and similar to that in humans. As noted previously, the lambda YAC taught by Popov and used by applicants is a small YAC and similar in size to that used in xenomouse I which had "human-like" ratios. Thus, based on the teachings of Mendez for xenomouse I which uses YACs closest in size to those taught by Popov and used by applicants, the ratio of human lambda to kappa light chains produced in the human lambda chain transgenic mouse does not appear to be "unexpected" since the skilled artisan reading Mendez et al. would have had a reasonable expectation that introducing small human light chain YACs into mice would alter the kappa/lambda light chain ratio to a more human ratio. Therefore, while the statements of Dr. Gonzalez Fernandez have been treated with deference, the evidence provided does not overcome the instant established case of *prima facie* obviousness.

Thus, for reasons of record as discussed in detail above, the rejection of 35-62 under 35 U.S.C. 103 stands.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the

technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER